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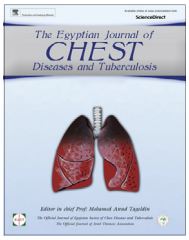

ORIGINAL ARTICLE

Methacholine challenge test as indicator for add on inhaled corticosteroids in COPD patients

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KEYWORDS

COPD;
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Abstract *Background:* Bronchial hyperreactivity (BHR) has been described in COPD. Inhaled corticosteroids (ICS) are used in the treatment of asthma, but the beneficial effects of steroid treatment in COPD are debatable. It has been suggested that inhaled corticosteroids are more likely to have beneficial effects in patients with COPD with more severe bronchial hyperresponsiveness.

Aim of the work: To investigate whether airway responsiveness to methacholine predicts response to add-on ICS treatment.

Subjects and methods: The study included 50 COPD patients stage I and stage II according to GOLD classification based on lung function and reversibility test. All cases were subjected to written informed consent, through history talking and clinical examination, chest X-ray, ECG and laboratory tests and methacholine challenge test. Then all patients were assessed by pulmonary function test, Clinical COPD Questionnaire (CCQ) and modified medical research council (MMRC) dyspnea scale. We added budesonide 800 mg daily with the previous medication for 6 months then patients were reevaluated again by the same tools used in the last visit.

Results: Our study showed that among 50 COPD patients with GOLD I or GOLD II classification 24 (48%) patients were positive for methacholine challenge test. Cases with positive methacholine test showed significant improvement regarding both CCQ and MMRC dyspnea scale with ICS treatment with no significant difference between both groups regarding pulmonary function tests.

Conclusion: The present study concluded that the presence of BHR to methacholine identifies patients with mild to moderate COPD who are likely to respond to ICS treatment.

Introduction

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations

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and comorbidities contribute to the overall severity in individual patients [1].

It is indeed rare to find a case of 'pure' COPD in the clinical setup. There are often patients in whom clinical picture overlaps with other respiratory disorders especially asthma. Consequently there are no rigid criteria to define and categorize COPD. One reason for this might be the existence of different clinical phenotypes of the disease. COPD presenting with bronchial hyperresponsiveness is possibly, one such phenotype [2].

Bronchial hyperresponsiveness (BHR) is defined as an "excessive bronchial narrowing and manifests itself as an exaggerated bronchoconstrictor response of the airways to various inhaled stimuli" [3]. Bronchial hyperreactivity (BHR) has been described in COPD [4], and it has been suggested that this increased response to provocative stimuli may be involved in the deterioration of lung function [5]. Characteristics of the BHR in COPD are not fully understood because of differences in methods and dose schedules of the provoking agent used by various investigators.

Inhaled corticosteroids (ICS) are used in the treatment of asthma, but the beneficial effects of steroid treatment in COPD are debatable. The improvements in lung function parameters, which are characteristic of steroid treatment in asthma, have not been unequivocally found in patients with COPD [6–7]. It has been postulated that, if steroids are important in the treatment of COPD, they act via downregulation of cytokine and adhesion molecule expression with a consequent reduction in cell migration and activation [8]. Approximately 25% of patients with stable COPD could benefit from continuous steroid treatment [8]. It has been suggested that inhaled corticosteroids are more likely to have beneficial effects in patients with COPD with more severe bronchial hyperresponsiveness [9].

Subject and methods

50 COPD patients GOLD I (mild) or GOLD II (moderate) were included in the study and the diagnosis of COPD was based on lung function and reversibility test as all patients showed obstructive pattern and reversibility less than 12%.

Study design

This multicenter study was conducted from January 2012 until January 2013 in outpatient clinic in both Tanta University and Cairo University to select patients with Gold I or Gold II and to assess bronchial hyperactivity in those patients, all the patients were subjected to the following after taking their written consent:

Through history taking and clinical examination, Chest X-ray, ECG and laboratory tests, Pulmonary function test and reversibility test and methacholine challenge test.

In methacholine challenge test we used five breath dosimeter protocol. After recording the baseline FEV1, the patient takes in five deep breaths of the lowest concentration of methacholine. FEV1 is recorded after the maneuvres. Higher concentrations of methacholine are used until fall in FEV1 is 20% or more.

The results are reported as 'PC20' or the concentration of methacholine at which FEV1 declined to 20% or less. It is interpreted as follows:

PC20 > 16 mg/ml = Normal BHR
PC20 4–16 mg/ml = Borderline BHR
PC20 1.0–4.0 mg/ml = Mild BHR (Positive test)
PC20 < 1.0 mg/ml = Moderate to severe BHR [10].

We collected 50 patients diagnosed as GOLD I or Gold II COPD patients and 24 patients of them showed positive methacholine challenge test. Then all patients with positive or negative methacholine challenge test were asked to receive tiotropium once daily for one month.

Then patients were divided into two groups: Group I with positive methacholine challenge test ($n = 24$) and group II with negative test ($n = 26$). Then all patients in were assessed by Pulmonary function test, Clinical COPD Questionnaire (CCQ) and modified medical research council (MMRC) dyspnea scale. We added budesonide 800 mcg daily with the previous medication.

CCQ is an individual's measurement of symptoms and functional state to quantify the impact of the disease on the daily life and well-being from the patient's point of view. It is formed of three domains (symptoms, functional and mental domain) [11].

CCQ is short (10 items) and easy to complete i.e. it is self-administered. It takes patients approximately 2 min to complete the questionnaire. Patients are instructed to recall their experiences during the previous week. They respond to each question using a 7-point scale from 0 = asymptomatic/no limitation to 6 = extremely symptomatic/totally limited.

After 6 months of ICS addition patients were reevaluated again by the same tools used in the last visit.

Results

Our study showed that among 50 COPD patients with GOLD I or GOLD II 24 (48%) patients were positive for methacholine challenge test.

Base line demographic data of both groups of patients showed no significant difference regarding age, sex, pulmonary function test and CCQ (Table 1).

After six months of treatment there was no significant difference in both groups regarding pulmonary function but group I showed significant improvement regarding both CCQ and MMRC dyspnea scale which is not found in group II (Tables 2 and 3).

Discussion

This multicenter trial investigated the effect of ICSs in steroid-naïve subjects with mild to moderate COPD and BHR to methacholine challenge. The results suggest that BHR often is present in patients with COPD (48%). This is consistent with Tashkin et al. [12], who found that about two-thirds of smokers with mild to moderate airflow limitation had BHR, expressed as PC20 (provocative concentration causing 20% decrease in FEV1). Our results also suggest that treatment with ICS is associated with a significant improvement in quality of life and reduction in dyspnea index.

Six months of high-dose ICS treatment were well tolerated but had no relevant impact on FEV1% predicted. But the impact was on quality of life, subjective degree of dyspnea, and respiratory symptoms. These results are in line with previous

Table 1 Demographic data.

	Group I (n = 24)		Group II (n = 26)		T-test	P-value
	Mean	±SD	Mean	±SD		
Age	55.87	3.155	54.425	2.155	1.904	0.062
	N	%	N	%	X^2	P-value
Sex						
Female	2	8.3	3	11.5	0.068	0.793
Male	22	91.7	23	88.5		
Gold						
Gold I	5	20.83	6	23.08	0.023	0.880
Gold II	19	79.17	20	76.92		

Table 2 Changes in CCQ, FEV1 and FEV1/FVC with ICS treatment for 6 months.

	Group I (n = 24)		Group II (n = 26)		T-test	P-value
CCQ						
Before	5.548	1.99	6.024	2.121	0.817	0.418
After	2.3	0.115	5.845	2.87	6.042	0.000*
Paired t-test (P)	0.002*		0.351			
FEV1% pred						
Before	83.65	16	84.24	15.15	0.134	0.894
After	85.15	14.214	86.15	12.54	0.529	0.599
Paired t-test (P)	0.670		0.725			
FEV1/FVC						
Before	0.63	0.11	0.64	0.15	0.267	0.790
After	0.665	0.15	0.65	0.11	0.405	0.687
Paired t-test (P)	0.318		0.441			

Table 3 Changes in MMRC dyspnea scale with ICS treatment for 6 months.

MRC	Group I				Group II			
	Before		After		Before		After	
	N	%	N	%	N	%	N	%
0	11	45.83	18	75.00	13	50.00	14	53.85
1	11	45.83	2	8.33	11	42.31	9	34.62
2	2	8.33	4	16.67	2	7.69	3	11.54
X^2	8.587				0.437			
P-value	0.013				0.803			

trials with regard to FEV1% predicted, quality of life (SGRQ), respiratory symptoms [13–16].

Current COPD GOLD guidelines recommend initiating treatment with long-acting bronchodilators prior to commencing add-on ICS, and the aim of the study was to investigate whether airway responsiveness to methacholine predicts response to add-on ICS treatment. Monotherapy with ICS alone is not recommended and would be of little interest to study. Furthermore, because of their differing pharmacologic actions, it is unlikely that tiotropium (a long-acting anticholinergic) masked steroid-induced (anti-inflammatory) effects.

Several large trials examining the effects of ICS in patients with moderate to severe COPD have shown an association with ICS use and improvement in quality of life [15,17–19]. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, for instance, showed a significant reduction in health status deterioration among patients receiving high-dose ICS compared with placebo [20]. In the present subjects with mild to moderate COPD, those with BHR showed a significant improvement in quality of life after 6 months of ICS treatment, likely because of the concomitant reduction in airway responsiveness to methacholine. Of note is that improvement in quality of life occurred despite the relative paucity of symptoms reported.

The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) demonstrated that asymptomatic, or silent, BHR measured by direct bronchoprovocation testing with methacholine was an increased risk factor not only for developing COPD but also for experiencing a new onset of symptoms, such as shortness of breath and cough [21]. Therefore, it can be argued that by treating BHR, symptoms and, therefore, quality of life can also be improved. Because it has been shown that BHR to methacholine is associated with sputum eosinophilia, it can be further hypothesized that ICS

reduces an underlying eosinophilic inflammation and, therefore, improves quality of life [21]. A limitation of the study might be the lack of data for sputum eosinophilia.

It should be mentioned that therapeutic response in patients with asthma was also observed for a paucigranulocytic phenotype of airway inflammation [22]. Mast cells are considered to both infiltrate the bronchial epithelium in COPD and to play an important role in the airway response to mannitol [23]. However, sputum analysis might not be the ideal method for detecting mast cells in bronchial airways [24].

Therefore, the present study provides evidence that the presence of BHR to methacholine identifies patients with mild to moderate COPD who are likely to respond to anti-inflammatory medication, and challenge test in mild to moderate COPD might be useful in selecting patients for ICS treatment. The connection between BHR and specific inflammatory processes in this subgroup needs further investigation.

Conflict of interest

None declared.

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